

AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, including listings, of claims in the application.

*Listing of Claims*

Claim 1 (currently amended): ~~A substantially pure~~ <sup>and purified</sup> An isolated  $\alpha$ -conotoxin peptide having the generic formula I: Xaa<sub>1</sub>-Xaa<sub>2</sub>-Xaa<sub>3</sub>-Xaa<sub>4</sub>-Xaa<sub>5</sub>-Cys-Cys-Xaa<sub>6</sub>-Xaa<sub>7</sub>-Xaa<sub>8</sub>-Xaa<sub>9</sub>-Cys-Xaa<sub>10</sub>-Xaa<sub>11</sub>-Xaa<sub>12</sub>-Cys-Xaa<sub>13</sub> (SEQ ID NO1:), wherein Xaa<sub>1</sub> is des-Xaa<sub>1</sub>, Ile, Leu or Val; Xaa<sub>2</sub> is des-Xaa<sub>2</sub>, Ala or Gly; Xaa<sub>3</sub> is des-Xaa<sub>3</sub>, Gly, Trp (D or L), neo-Trp, halo-Trp or any unnatural aromatic amino acid; Xaa<sub>4</sub> is des-Xaa<sub>4</sub>, Asp, Phe, Gly, Ala, Glu,  $\gamma$ -carboxy-Glu (Gla) or any unnatural aromatic amino acid; Xaa<sub>5</sub> is Glu, Gla, Asp, Ala, Thr, Ser, Gly, Ile, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa<sub>6</sub> is Ser, Thr, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa<sub>7</sub> is Asp, Glu, Gla, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa<sub>8</sub> is Ser, Thr, Asn, Ala, Gly, Arg, Lys, ornithine, homoarginine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, His, halo-His, Pro or hydroxy-Pro; Xaa<sub>9</sub> is Thr, Ser, Ala, Asp, Asn, Pro, hydroxy-Pro, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa<sub>10</sub> is Gly, Ser, Thr, ~~Ala~~, Asn, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa<sub>11</sub> is Gln, Leu, His, halo-His, Trp (D or L), halo-Trp, neo-Trp, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid or any unnatural aromatic amino acid; Xaa<sub>12</sub> is Asn, His, halo-His, Ile, Leu, Val, Gln,

Application No.: 09/493,795  
Amendment Dated 20 January 2004  
Reply to Office Action of 18 July 2003

Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa<sub>13</sub> is des-Xaa<sub>13</sub>, Val, Ile, Leu, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; and the C-terminus contains a free carboxyl group or an amide group and

wherein (a) the unnatural aromatic amino acid is selected from the group consisting of nitro-Phe and 4-substituted-Phe wherein the substituent is C<sub>1</sub>-C<sub>3</sub> alkyl, carboxyl, hydroxymethyl, sulphomethyl, halo, phenyl, -CHO, -CN, -SO<sub>3</sub>H and -NHAc, (b) the unnatural hydroxy containing amino acid is selected from the group consisting of such as 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr and (c) the unnatural basic amino acid is selected from the group consisting of N-1-(2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolinyl]-Gly and 2-[3-(2S)pyrrolinyl]-Ala.

Claim 2 (currently amended): ~~A substantially pure~~ <sup>and purified</sup> An isolated  $\alpha$ -conotoxin peptide of generic formula I (SEQ ID NO:1) selected from the group consisting of:

a peptide comprising the amino acid sequence Ala-Cys-Cys-Ser-Asp-Arg-Arg-Cys-Arg-Xaa<sub>3</sub>-Arg-Cys (SEQ ID NO:5), wherein Xaa<sub>3</sub> of SEQ ID NO:5 is Trp (Der L), halo-Trp or neo-Trp and the C-terminus contains a carboxyl or amide group; and

a derivative of the peptide of SEQ ID NO:5 thereof;

wherein said derivative comprises an amino acid substitution of the peptide of SEQ ID NO:5 selected from the group consisting of (a) an Arg residue is substituted with Lys, ornithine, <sup>homoarginine</sup> ~~homoarginine~~, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or an unnatural basic amino acid selected from the group consisting of N-1-(2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolinyl]-Gly and 2-[3-(2S)pyrrolinyl]-Ala, (b) Xaa<sub>3</sub> is substituted with an unnatural aromatic amino acid selected from the group consisting of nitro-Phe and 4-substituted-Phe wherein the substituent is C<sub>1</sub>-C<sub>3</sub> alkyl, carboxyl, hydroxymethyl, sulphomethyl, halo, phenyl, -CHO, -CN, -SO<sub>3</sub>H or -NHAc, (c) an Asp residue is substituted with a tetrazolyl

Application No.: 09/493,795  
Amendment Dated 20 January 2004  
Reply to Office Action of 18 July 2003

derivative or Gly or a tetrazolyl derivative of Ala, (d) a Ser residue is substituted with Thr, (e) a Cys residue is substituted with a D-Cys or a homocysteine (D or L), or (f) a pair of Cys residues is replaced pairwise with Ser/(Glu or Asp) or Lys (Glu or Asp) Xaa, is Trp (D or L), halo-Trp or neo-Trp; and the C-terminus contains a carboxyl or amide group.

Claims 3-7 (canceled).

Claim 8 (currently amended): The isolated ~~substantially pure~~  $\alpha$ -conotoxin peptide of claim 1, which is modified to contain an O-glycan, an S-glycan or an N-glycan.

Claim 9 (currently amended): The isolated ~~substantially pure~~  $\alpha$ -conotoxin peptide of claim 2 which is modified to contain an O-glycan, an S-glycan or an N-glycan.

Claims 10-38 (canceled).

Claim 39 (currently amended): ~~A substantially pure~~ <sup>and purified</sup> An isolated  $\alpha$ -conotoxin protein precursor comprising the amino acid sequence Phe Asp Gly Arg Asn Ala Pro Ala Asp Asp Lys Ala Ser Asp Leu Ile Ala Gln Ile Val Arg Arg Ala Cys Cys Ser Asp Arg Arg Cys Arg Trp Arg Cys Gly (SEQ ID NO:236).

Claims 40-41 (canceled).